How I treat monoclonal gammopathy of renal significance (MGRS)

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Abstract

Recently, the term monoclonal gammopathy of renal significance (MGRS) was introduced to distinguish monoclonal gammopathies that result in the development of kidney disease from those that are benign. By definition, patients with MGRS have B cell clones that do not meet the definition of multiple myeloma or lymphoma. Nevertheless, these clones produce monoclonal proteins that are capable of injuring the kidney resulting in permanent damage. Except for immunoglobulin light chain (AL) amyloidosis with heart involvement where death can be rapid, treatment of MGRS is often indicated more to preserve kidney function and prevent recurrence after kidney transplantation rather than the prolongation of life. Clinical trials are rare for MGRS related kidney diseases except in immunoglobulin light chain (AL) amyloidosis. Treatment recommendations are therefore based on the clinical data obtained from treatment of the clonal disorder in its malignant state. The establishment of these treatment recommendations is important until data can be obtained by clinical trials of MGRS related kidney diseases.
Introduction

Monoclonal gammopathy of renal significance (MGRS) is defined by the causal relationship between a small B cell clone and renal disease, usually through deposition of the secreted monoclonal immunoglobulin (MIg), or a fragment thereof. The spectrum of MGRS is evolving, with the recent description of novel entities. With the exception of immunoglobulin light chain (AL) amyloidosis, few studies have focused on therapeutic issues. The International Kidney and Monoclonal Gammopathy Research Group (IKMG) initiated a collaborative effort aimed at delineating treatment strategies.

What is MGRS?

The B cell clone corresponds to the definition of a “dangerous small B cell clone”, suggesting that its deleterious consequences are not directly related to cellular proliferation but to other mechanisms, such as MIg deposition. Accordingly, myeloma cast nephropathy (MCN), which almost invariably complicates high tumor mass myeloma, should not be included in MGRS. Most MGRS are due to deposition of a MIg fragment with distinct localization and pattern of ultrastructural organization. This results in glomerulopathies with organized deposits, either fibrillar (AL, immunoglobulin heavy chain [AH] and immunoglobulin light and heavy chain [ALH] amyloidosis), microtubular (type I and type II cryoglobulinemias, immunotactoid glomerulopathy [ITG]) or non-organized deposits (Randall type monoclonal Ig deposition disease [MIDD] and non-Randall type proliferative glomerulonephritis with monoclonal Ig deposits [PGNMID]). MGRS also includes tubular disorders such as Fanconi syndrome (FS). Non-amyloid fibrillary glomerulonephritis should not be considered as MGRS because it is nearly always characterized by polyclonal IgG deposits without a detectable clonal B cell disorder. In MGRS, deposits of different ultrastructural patterns derived from the same MIg can occur. For instance, fibrillar AL and amorphous Randall-type deposits can coexist in the same patient. In most cases, the overall
survival of patients with MGRS is significantly better than that of multiple myeloma, but the renal outcomes are not. The exception is patients with AL amyloidosis particularly those with cardiac involvement where death can occur rapidly. Many patients who develop end stage renal disease (ESRD) are often not considered for kidney transplantation due to their high rates of recurrence.

In a patient in whom MGRS is suspected, it is essential to assess i) the characteristics of monoclonal gammopathy, particularly its isotype and whether it corresponds to an overt lymphoid and/or plasmacytic disorder and ii) the type of nephropathy and its impact on renal function. In addition, it is mandatory to carefully search for extra-renal manifestations. To accurately characterize the renal disease, a kidney biopsy with detailed immunofluorescence (IF) and electron microscopic (EM) studies to identify deposit composition and pattern of organization is needed in most cases. The one exception is AL amyloidosis which can be diagnosed if AL deposits can be demonstrated in other tissues such as fat.

Which therapeutic options?

Treatment of the B cell clone

To date, no strategy is available to inhibit M1g tissue deposition, or to directly clear the already deposited material. Innovative strategies that are currently in early clinical testing include small molecule weight inhibitors of serum amyloid P protein (SAP) and monoclonal antibody against neoepitope on immunoglobulin light chains. Thus, targeting the underlying B cell clone with chemotherapy, although it is not an evidently malignant clone per se, is the only available therapeutic option for MGRS.

The choice of chemotherapeutic agents should take into account their renal metabolism and potential renal and extra-renal toxicity. For alkylating agents, cyclophosphamide is preferred to melphalan due to its lower toxicity in patients with reduced
kidney function.\textsuperscript{10} Similarly, within the immunomodulatory drug class (IMiD), thalidomide may be more appropriate than lenalidomide since the latter is in part cleared renally and may also sometimes worsen renal function in certain disease states notably in AL amyloidosis.\textsuperscript{11,12} In contrast, bortezomib can be used without dose adjustment with a good tolerance profile, including in the setting of end-stage renal disease (ESRD).\textsuperscript{13-15} The risk of peripheral neuropathy remains a concern, but has been shown to be reduced by weekly administration and the use of the sub-cutaneous route of administration in patients with myeloma.\textsuperscript{16} Bendamustine, which has been proposed for the treatment of various lymphoid disorders, has also a predominantly non-renal metabolism and can be given to patients with ESRD.\textsuperscript{17,18} Among nucleoside analogs, fludarabine requires dose adaptation and should be avoided in patients with renal failure.\textsuperscript{19} The use of rituximab and other anti-CD20 monoclonal antibodies raises no concerns in patients with renal impairment, including ESRD.\textsuperscript{20,21}

High dose melphalan (HDM) supported by autologous peripheral blood stem cell transplantation (ASCT) may be a therapeutic option in some patients. It is essential to collect stem cells early in the course of the treatment, avoiding excessive prior use of drugs with potential stem cell damage, such as melphalan and lenalidomide. HDM/ASCT is feasible in MM patients with renal failure, even requiring dialysis.\textsuperscript{22-24} However, mortality and morbidity, including the risk of worsening renal function, increases with the severity of renal impairment.\textsuperscript{25-27} Melphalan dose should be adjusted in patients with chronic kidney disease (CKD) stage 3 or above and risk/benefit ratio should be carefully evaluated in each case.

The underlying plasma cell clone responsible for MGRS may manifest as a solitary plasmacytoma. Although this situation is rare, it has key therapeutic implications. Local radiotherapy may result in a complete and sustained control of the MIg production and, consequently, of its renal consequences.\textsuperscript{28} The initial work-up of MGRS should include a
complete skeletal survey using conventional X-rays, and magnetic resonance imaging or PET-scan may be required for imaging suspected mass lesions or a solitary plasmacytoma.

In MGRS, assessment of hematological response is crucial. It depends upon the evaluation of the M1g component that is responsible for renal lesions. In AL amyloidosis, measurement of serum free light chain (FLC) provides an essential tool. Current response criteria in AL amyloidosis distinguishes complete response (normal FLC ratio and negative serum and urine immunofixation), very good partial response (difference between involved and uninvolved FLCs \( d\text{FLC} < 40 \text{ mg/L} \)), partial response (\( d\text{FLC} \) decrease > 50%), and no response.\(^{29}\) The use of the same criteria in all types of MGRS due to the deposition of monoclonal light chain (LC), particularly LCDD and Fanconi syndrome is logical. In MGRS involving an intact M1g, the criteria recommended in MM should be applied.\(^{30}\) When the causal M1g is not detectable or difficult to measure, evaluating the cellular response, usually by repeated bone marrow examination, is the only way to assess the hematological efficacy of treatment. In all cases, renal (and extra-renal, if present) response should be regularly monitored, bearing in mind that it is usually delayed and depends on the quality of the hematological response.\(^{31}\) Whether new molecular or cytometric techniques are useful to detect residual disease and impact outcomes deserves further investigation.\(^{32}\)

In all MGRS subtypes, evidence for relapse of the underlying clonal disease should prompt the clinician to reinitiate therapy, based on criteria similar to the ones applied for the initiation of primary therapy. Treatment choice should take into account characteristics of the first response, toxicity of prior therapies, general status and renal function.

_Treatment of renal disease_

MGRS should be monitored according to usual best practices including, for example, thrombotic and infectious risk prevention in case of nephrotic syndrome. Except in AL
amyloidosis, hypertension and proteinuria should be controlled, preferably using blockers of the renin-angiotensin system. In patients with FS, bicarbonate, phosphate and vitamin D supplementation should be given to prevent osteomalacia. For AL amyloidosis, introduction of an ACE or ARB should only be considered only in patients who are hypertensive given these patients’ tendency towards orthostatic hypotension.

MGRS should not be considered as a contra-indication to renal transplantation since the risk of patients dying from their clone is low. However there are no data to suggest that small B cell clones are truly curable, thus the risk of disease recurrence does expose the graft to risk of failure. This can occur after a variable delay depending on each type of renal disease. Whereas recurrence of AL amyloidosis usually slowly impacts graft function, graft loss rapidly occurs in most patients with PGNMID. Reducing the level of the MIg by obtaining the best hematological response is a critical issue in allograft survival. Although this ideally means stringent complete response, a renal transplant may be considered in patients who are not in hematological CR and have no cardiac involvement. This must be discussed in each individual case, particularly taking into account the estimated time before the expected deterioration of renal function that could likely be irreversible. During post-transplant follow-up, careful surveillance of MIg parameters is mandatory. Reintroduction of therapy should be considered upon progression of the clonal disorder. Thus, the decision for renal transplantation should be taken considering the underlying MGRS characteristics, initial therapeutic response, presence of extra-renal manifestations and patient’s status. The risk of graft loss, its link with the B cell clone and the potential need for reintroduction of chemotherapy should be clearly explained to the recipient (and to the donor, if a living donor transplantation is considered).
AL (AH and ALH) amyloidosis

AL (AH and ALH) amyloidosis is usually associated with a low-grade plasma cell clone, most often secreting lambda LC. The amyloid in AL is composed of monoclonal immunoglobulin light chains while it is composed of monoclonal immunoglobulin heavy chains in AH and ALH contains the entire immunoglobin. Renal involvement is present in about 70% to 80% of patients and extra-renal manifestations are frequent. Approximately 75% of all AL patients present with proteinuria with 36% in the nephrotic range. Elevated creatinine is noted in over half of the patients. Since the kidney is not an important contributor to early mortality in these patients, the type of treatment used is guided by the degree of cardiac involvement, as assessed by cardiac biomarkers. At the start of the 21st century, patients were now classified according to Mayo Clinic criteria as stage I, II, or III, depending on whether the NT-proBNP and troponin T levels are both low (< 332 ng/L and 0.035 µg/L), are high for only one level, or are both high, respectively. More recently, the level of immunoglobulin FLC was added to the criteria with minor modifications of cut-points and inclusion of FLC burden. Achieving the best and most durable hematological response is the goal of therapy and must be adapted to patients who are often very fragile. The more severe the cardiac disease, the quicker response should be obtained. Since direct myocardial toxicity of amyloidogenic LC has been documented, rapid suppression of involved FLC is an important prognostic factor, particularly in patients with stage III cardiac disease.

Current recommendations can be summarized as follows:

- In patients with stage I-II disease, first line treatment should be based on Melphalan + Dexamethasone (M-Dex). It is likely that reinforcing this regimen with bortezomib increases hematological and organ response rate. This is currently under investigation through an international phase III trial comparing M-
Dex to M-Dex plus bortezomib (NCT01277016). Until the results of this study are available, the current approach is to rapidly introduce bortezomib, after one or two courses of M-Dex in the absence of a clonal response. In patients with advanced CKD, cyclophosphamide is preferred to melphalan, and regimens such as Cyclophosphamide-Bortezomib-Dexamethasone (CBD also referred to as CyBorD or VCD) have demonstrated their efficacy. Another option is to use thalidomide instead of bortezomib (CTD regimen).

- Patients with stage III cardiac involvement represent a therapeutic challenge since their median survival remains poor. Preliminary encouraging results have been obtained using the CBD regimen, which seems to significantly reduce the early death rate based on small case series. In young selected patients, cardiac transplantation can be considered, preferably after hematological remission has been achieved.

- In selected patients (mainly stage I and II disease), HDM/ASCT should be considered, in the absence of overt renal insufficiency and of other advanced organ failure.

**Randall-type monoclonal Ig deposition disease (MIDD)**

In MIDD, like AL, the monoclonal gammopathy may occasionally be an overt myeloma (>10% bone marrow plasma cells with at least one myeloma defining event); however, in MIDD, the clone more often secretes kappa LC. Renal involvement is nearly constant and usually manifests with high-grade proteinuria, hematuria, hypertension and renal insufficiency. Extra-renal manifestations, particularly cardiac and hepatic, are not uncommon but rarely symptomatic. The most frequent form of MIDD is light chain deposition disease (LCDD). IF study of the kidney biopsy is mandatory for the diagnosis, showing typical linear amorphous LC deposits along the tubular basement membranes. Glomerular and vascular
deposits are usually associated, with a pattern of nodular glomerulosclerosis in two thirds of patients with LCDD.\textsuperscript{58-61} Heavy chain deposition disease (HCDD) and light and heavy chain deposition disease (LHCDD) are rare and should be managed similarly to LCDD.\textsuperscript{62,63}

As MIDD is rare, controlled studies are lacking and the therapeutic approach is based on consensus opinion. Achieving the best hematological response appears to be as important as in AL. It may result in regression of M\textit{I}g tissue deposits, providing that complete and sustained remission has been obtained.\textsuperscript{64,65}

Small retrospective series suggested that HDM/ASCT is a good therapeutic option, with high hematological response rates and low treatment related mortality (TRM). This contrasts with AL amyloidosis in which patients are much more fragile with frequent systemic complications that increase TRM.\textsuperscript{64-71} Data regarding HDM/ASCT have been published before the era of novel anti-myeloma agents. Preliminary results suggest that bortezomib-based regimens could produce hematological response rates similar to those obtained with HDM/ASCT, as is the case in MM.\textsuperscript{72-77}

Taking into account these points, therapeutic recommendations should be based on the degree of renal impairment:

- In patients with CKD stages 1-3, the main goal of treatment is preserving kidney function. The panel recommends the use of a bortezomib-based regimen, such as CBD, as front line. HDM/ASCT should then be considered in selected patients with good performance status and no significant extra-renal manifestations, particularly when they have achieved only partial hematological response to the initial treatment.

- In patients with CKD stages 4 and 5, the probability of renal recovery is low. In patients not eligible for renal transplantation, the main goal of the treatment is
preserving extra-renal organs, particularly the heart. The panel recommends a bortezomib-based regimen, such as CBD. If a renal transplantation is planned, the therapeutic goal is the preservation of long-term allograft function, which requires an optimal clonal response.\textsuperscript{59,78} Accordingly, HDM/ASCT should be considered after a 3 to 4 cycles of a CBD-like regimen.

**Type I cryoglobulinemia**

Monoclonal Ig may precipitate under cold exposure, thus defining cryoglobulinemia. Type I cryoglobulins are composed of a single MIg.\textsuperscript{79} A serum rheumatoid factor (RF) is typically not detected and complement abnormalities are not constant. Type I cryoglobulinemia may be asymptomatic or cause cold-triggered ischemic symptoms, predominantly cutaneous (Raynaud’ phenomenon).\textsuperscript{80} Articular manifestations are mostly observed when the cryoglobulin (usually an IgG3) precipitates as crystals (crystal-cryoglobulinemia).\textsuperscript{81,82} Renal manifestations are more common with IgG type I cryoglobulin and less frequent with IgM.\textsuperscript{82,83} It typically manifests as chronic glomerular disease with flares characterized by nephritic syndrome, acute renal insufficiency and severe hypertension. Histologically, the hallmark of the disease is membranoproliferative glomerulonephritis with glomerular thrombi and microtubular deposits made up of the monoclonal cryoglobulin.\textsuperscript{82,83}

Type I cryoglobulinemia may be observed in patients who would otherwise be classified as MGUS based on level of clonal burden, MM, WM or any other type of B-cell lymphoid disorder secreting an entire MIg.\textsuperscript{82,84} Patients should carefully avoid cold exposure and take appropriate protective measures. As data regarding management of this rare condition are scarce, the following recommendations are only guided by the panel experience:
In patients with few systemic symptoms and a low-grade underlying B-cell proliferation, observation alone is recommended, including serial assessment of renal parameters, since renal manifestations may occur secondarily.

In patients with symptomatic and/or progressive systemic disease, particularly in the presence of renal complications, therapy is indicated and should be selected based on the underlying clone:

- If it is plasmacytic, usually secreting a monoclonal IgG (or IgA), treatment should rely on anti-myeloma agents. In patients with renal failure, bortezomib, cyclophosphamide and/or thalidomide-based regimens should be used. Rituximab is not indicated. In selected patients, HDM/ASCT may be considered.

- If it is lympho-plasmacytic, usually associated with a monoclonal IgM, the treatment should be that of WM, currently based on Rituximab-containing regimens.

- If the underlying disease is chronic lymphocytic leukemia (CLL) or a B-cell lymphoma of any type, the treatment should be adapted accordingly.

In all cases, bendamustine, which is not eliminated by the kidney, is likely to be a good alternative. In patients with acute severe systemic symptoms, complete plasma exchange is indicated in addition to chemotherapy.82-84

**Type II cryoglobulinemia**

Type II “mixed” cryoglobulins are composed of a MIg, usually an IgM kappa with a RF activity, associated with polyclonal Ig. A serum RF is always detectable and serum complement levels are constantly decreased. Type II cryoglobulinemia is often a silent
condition. When symptomatic, vascular purpuric lesions are nearly always present. Other manifestations are usually related to small vessel vasculitis, including arthralgias and/or peripheral neuropathy. Disease flares are common and more often triggered by activity and orthostatism than by cold exposure. Clinical and pathological renal manifestations are close to that observed in type I cryoglobulinemia. However, IF studies show that glomerular deposits contain both the monoclonal IgM and polyclonal IgG along with complement components.

Most cases are associated with chronic hepatitis C virus (HCV) infection. Other conditions include hepatitis B virus infection and autoimmune disorders, particularly Sjögren’s syndrome. In all cases, type II cryoglobulinemia implicates the presence of an underlying B-cell clone most typically a very small clone with less than 10% bone marrow involvement. An overt lymphoid proliferation, usually a WM or a low-grade lymphoma, can be detected initially or may develop during follow-up.

The knowledge of whether or not type II cryoglobulinemia is associated with HCV infection is imperative to guide treatment. Accordingly, HCV testing infection should be systematic, including serum HCV RNA detection, and genotyping if present.

In the absence of prospective studies, treatment strategy may be summarized as follows:

- Antiviral therapy, usually combining pegylated alpha interferon and ribavirin should be given to all patients with symptomatic type II cryoglobulinemia associated with chronic HCV infection. Antiviral therapy may be given alone in patients who have only a few symptoms, i.e. episodic flares of vasculitic purpura. In those with more symptomatic vasculitis, antiviral therapy should be combined with rituximab. In addition, in patients with rapidly progressive renal disease and/or other severe organ involvement, total plasma exchange should be considered. Importantly, because of their remarkable symptomatic
efficacy, high-dose steroids should be added in all cases with overt vasculitis. Due to the risk of their side effects, one should avoid long-term administration of steroids if possible.88,89

- In those patients with no detectable viral replication, who present with episodic purpuric flares, surveillance only is recommended. In case of recurrent symptoms or of renal involvement, rituximab is the treatment of choice.90

- In all patients with overt WM or B-cell lymphoma, chemotherapy should be considered in patients with symptoms more significant than occasional purpura regardless of their HCV status. The regimen should be defined taking into account the type of the underlying B-cell clone and the level of renal function (see above).91

**Immunotactoid glomerulopathy (ITG)**

ITG, also referred to as glomerulonephritis with organized microtubular monoclonal Ig deposits (GOMMID) is a rare glomerular disease with proteinuria, frequent nephrotic syndrome, hematuria, CKD and hypertension. Extra-renal manifestations are uncommon. Glomerular lesions are usually characterized by atypical membranous and MPGN patterns. By IF, glomerular deposits are composed of monotypic IgG and complement components. EM, which is required for the diagnosis, shows a typical organization of deposits into microtubules of 10 to 60 nm in diameter, arranged in parallel bundles.3,5,6,92 Similar microtubular inclusions may be observed in the cytoplasm of the circulating and medullary clonal B-cell population.3,5

Importantly, the underlying B-cell lymphoid disorder is a CLL or a small lymphocytic lymphoma in more than half of the cases. A low-grade plasma cell clone is less frequent.5,92 Accordingly, the initial workup should include a careful search for a clonal B-cell population among peripheral blood and bone marrow lymphocytes, including phenotypic and Ig gene rearrangement studies.
Although therapeutic choice relies upon few small case series, a CLL-adapted treatment may be proposed in most patients. In case of severe CKD, cyclophosphamide and/or bendamustine-based regimens including corticosteroids may be recommended. The addition of rituximab should be considered in patients with overt CLL. In patients with gammapathy only, the role of rituximab is questionable and bortezomib-based therapy may be considered.\textsuperscript{5,92}

**Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID)**

PGNMID is a recently described entity that should be distinguished from Randall-type MIDD. Both diseases are featured by glomerular non-organized M\textsubscript{I}g deposits. However, in PGNMID, deposits usually consist of an entire M\textsubscript{I}g (most commonly IgG\textsubscript{3}κ), with a granular non-linear appearance by IF and EM, without detectable deposits along tubular basement membranes and around vascular myocytes. Various patterns can be observed, including mesangial, atypical membranous and membranoproliferative GN. Globally, PGNMID resembles an immune complex-like GN, but with monotypic Ig deposits, a feature that should draw the pathologist’s attention.\textsuperscript{93-96}

Extra-renal manifestations are rare and PGNMID appears as a renal limited disorder, with prominent glomerular symptoms and frequent CKD. Importantly, sensitive techniques including nephelometric tests for FLCs can detect a serum and urine M\textsubscript{I}g in approximately one third of patients only. A monoclonal proliferation of plasma cells in the bone marrow is found in less than 10\% of patients.\textsuperscript{93-96}

Some authors are reluctant to recommend chemotherapy in PGNMID with no detectable M\textsubscript{I}g. However, monotypic glomerular deposits are the result of a circulating M\textsubscript{I}g, which indicates the presence of an underlying B-cell disorder. Consequently, PGNMID almost always recurs after renal transplantation.\textsuperscript{37,97}
The panel recommends adapting the therapeutic approach to the severity of renal disease:

- In patients with CKD stages 1-2, proteinuria of less than 1g/day and no evidence of progressive disease, symptomatic measures only may be advised with careful surveillance. In such cases, occasional spontaneous renal remissions may occur.

- In patients with CKD stages 1-2 and high-grade proteinuria (over 1g/day) or progressive disease, and in patients with CKD stages 3-4, chemotherapy is indicated. Cyclophosphamide and bortezomib are the drugs of choice, and a CBD-like regimen is a good option. In some patients aged less than 65 years, HDM/ASCT may be performed. Preliminary reports suggest a beneficial effect of rituximab, including in patients without a detectable B-cell clone. However, it seems reasonable proposing rituximab only to patients in whom an associated CD-20 positive B-cell clone can be demonstrated.

- In patients with CKD stage 5 who are candidates for renal transplantation, the achievement of a complete hematological remission is a key goal for patients with a detectable monoclonal gammopathy. Thus, HDM/ASCT should be strongly considered. For those who never had a detectable monoclonal gammopathy or plasma cell clone, there is no consensus regarding their treatment prior to kidney transplant. In contrast, in patients ineligible for renal transplantation, the benefit of chemotherapy is highly questionable and conservative treatment should be recommended.

**Acquired Fanconi syndrome (FS)**

Acquired FS is characterized by proximal tubular dysfunction secondary to accumulation of monoclonal κ LCs crystalline inclusions within the endolysosomal
compartment of proximal tubular cells. Similar LC inclusions can be detected in the cytoplasm of associated clonal plasma cells. FS typically complicates MGUS or a low-grade MM which is almost always of the kappa class.\textsuperscript{4,33,98,99} Few cases have been described in WM.\textsuperscript{100} Most patients present with moderate CKD, with unusual hypophosphatemia and hypouricemia which should prompt to search for other signs of proximal tubule dysfunction, particularly generalized aminoaciduria. Of note, the urine phosphate leak frequently causes osteomalacia and subsequent bone pain should not be misinterpreted as secondary to myeloma.

Other extra-renal manifestations are absent in typical FS. However, FS may be part of the so-called crystal-storing histiocytosis (CSH), which is characterized by the accumulation of LC crystals, not only in proximal tubular cells but also in lysosomes of histiocytes of bone marrow. In addition, CSH can involve various tissues including spleen and lymph nodes, sometimes in the context of systemic symptoms with macrophage activation.\textsuperscript{101,102}

Very few series of LC-associated FS have been published and the efficacy of the so-called novel anti-myeloma agents has not been evaluated. In most cases, FS appears to slowly progress toward ESRD and rarely symptomatic myeloma.\textsuperscript{33,98} Accordingly, therapeutic decisions should take into account treatment side effects, particularly the potential risk of secondary myelodysplastic syndrome from alkylating agents.\textsuperscript{98}

Symptomatic measures to prevent osteomalacia are mandatory. All patients with an associated overt lymphoid disorder should receive appropriate chemotherapy. For the rare patients with symptomatic CSH, steroids should be considered in addition to chemotherapy. Otherwise, treatment choices should be adapted to the degree of renal failure:

- In patients with CKD stages 1-3, chemotherapy should be considered to try to slow progression to ESRD. Cyclophosphamide,
bortezomib or thalidomide based regimens are the best options. Bendamustine may also be utilized. HDM/ASCT may be performed in selected non-responding patients, although the benefit of this strategy remains to be proven.

- In patients with CKD stages 4-5 who are eligible for renal allograft, chemotherapy, including HDM/ASCT should be considered either prior and/or after transplantation. In patients who will not be candidate for renal transplantation, there is no benefit to introduce chemotherapy.

**Miscellaneous**

In addition to kidney deposition of a M1g, other mechanisms may induce renal lesions in MGRS. They may involve the secretion of various biological factors and/or autoantibody activity of the M1g.

The so-called POEMS syndrome can include renal manifestations, usually featured by vascular and glomerular thrombotic microangiopathy including mesangiolysis. These are considered to be due to the secretion of vascular endothelial growth factor by the clonal cells or their environment, which is a hallmark of this syndrome. Whether the causal plasmacytic proliferation is localized or not is the key point for therapeutic decisions.103

A novel MGRS entity characterized by glomerulonephritis with isolated glomerular C3 deposits has been recently described. It is associated with a circulating monoclonal IgG, most often with MGUS or indolent MM. Hypocomplementemia secondary to activation of the complement alternative pathway (CAP) is usual, in the absence of detectable anti-C3 convertase activity (nephritic factor). Autoantibody activity of the M1g against a CAP
regulatory protein is the main current hypothesis. Since the disease course is rapid, with a high risk of recurrence after renal transplantation, chemotherapy should be given early.\textsuperscript{104,105}

**Conclusion**

Current treatment of MGRS is based on therapies targeting the causal B-cell clone with treatment choices based on extrapolation of treatments used for the equivalent overt malignancy. Therapeutic choices should take into account the renal characteristics of the disease, particularly the risk of CKD progression, the presence and severity of extra-renal manifestations and the safety profile of anti-neoplastic drugs in renal impairment. Early diagnosis, when renal function is still preserved, usually facilitates treatment management and results in better long-term outcome. Since MGRS is a heterogeneous and relatively rare entity, a common effort of both nephrologists and hematologists inside well-designed prospective collaborative studies is required to improve management.

**Author Contributions**

JPF, FB, RAK, EK, BW, MD, AD, NL all contributed to the planning and writing of this manuscript.

**Conflict of Interest**

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